chain bonds :
2-18 3-24 4-26 7-14 8-15 9-25 11-16 17-21
ring bonds :
1-2 1-6 1-13 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10 10-11 11-12 12-13
18-19 18-23 19-20 20-21 21-22 22-23
exact/norm bonds :
1-13 2-18 5-7 6-10 7-8 7-14 8-9 9-10 10-11 11-12 12-13 18-19 18-23
19-20 20-21 21-22 22-23
exact bonds :
3-24 4-26 8-15 9-25 11-16 17-21
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:Atom 19:Atom
20:Atom 21:Atom 22:Atom 23:Atom 24:CLASS 25:CLASS 26:CLASS
fragments assigned product role:
containing 1

Stereo Bonds:

16-11 (Single Wedge).

Stereo Chiral Centers:

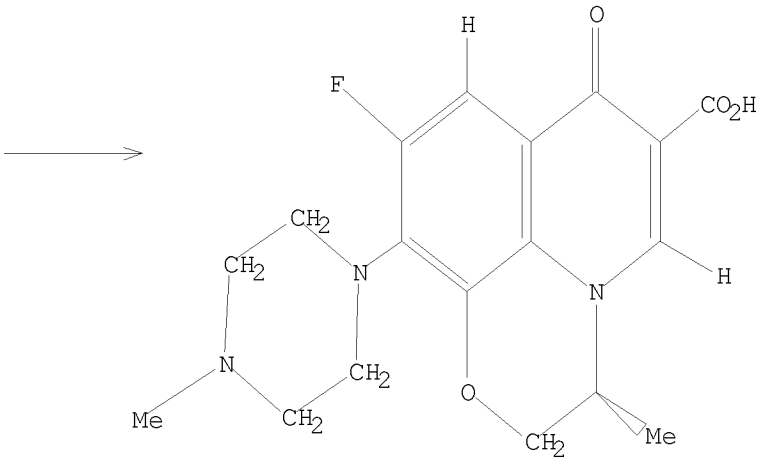
11 (Parity=Don't Care)

Stereo RSS Sets:

Type=Relative (Default). 1 Nodes= 11

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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=> file casreact
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.48       0.70

FILE 'CASREACT' ENTERED AT 08:35:42 ON 24 JUN 2009
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FILE CONTENT:1840 - 21 Jun 2009 VOL 150 ISS 26

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************************************************************
*                                                          *
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*                                                          *
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This file contains CAS Registry Numbers for easy and accurate substance
identification.

=> s l1
SAMPLE SEARCH INITIATED 08:35:45 FILE 'CASREACT'
SCREENING COMPLETE -       32 REACTIONS TO VERIFY FROM        6 DOCUMENTS

100.0% DONE      32 VERIFIED       1 HIT RXNS                      1 DOCS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED VERIFICATIONS:       301 TO      979
PROJECTED ANSWERS:               1 TO       79

L2            1 SEA SSS SAM L1 (     1 REACTIONS)

=> s l1 sss full
FULL SEARCH INITIATED 08:35:56 FILE 'CASREACT'
SCREENING COMPLETE -     2479 REACTIONS TO VERIFY FROM      137 DOCUMENTS
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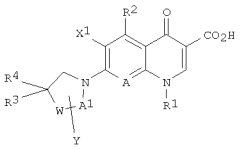
L3 ANSWER 1 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 149:493695 CASREACT
TITLE: Method for producing quinolonecarboxylic acid derivatives
INVENTOR(S): Sato, Koji; Sakuratani, Kenji
PATENT ASSIGNEE(S): Daiichi Sankyo Company, Limited, Japan
SOURCE: PCT Int. Appl., 32pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008126384	A1	20081023	WO 2008-JP817	20080331

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: JP 2007-90650 20070330
OTHER SOURCE(S): MARPAT 149:493695
GI

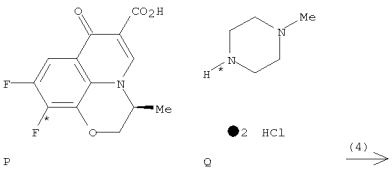


I

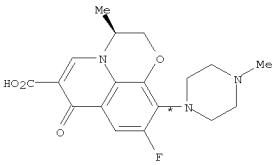
AB The title compds. I [A1 = (CH2)n; R1 = (un)substituted alkyl, (un)substituted cycloalkyl, (un)substituted Ph, etc.; R2 = (un)substituted amino, H, alkyl, etc.; X1 = H, halo; A = N, CX2; X2 = H, cyano, halo, etc.; X2 and R1 and a part of the main nucleus may be united to form an (un)substituted ring; W = CHR5, O, NR6; R5 = H, halo, (un)substituted alkyl, etc.; R6 = H, alkyl, cycloalkyl; Y = H, alkyl, amino (connected to an optional C atom on the satd. hetero ring), etc.; n = 0 - 2; R3, R4 = H, halo, (amino-substituted) cycloalkyl, etc.; further details related to R3 and R4 are given] are prepd. by reaction of a haloquinolonecarboxylic acid deriv. with a cyclic amine salt and a boron deriv. in a solvent in the presence of a base. I are antibacterials (no data). Thus,

1-cyclopropyl-1,4-dihydro-6-fluoro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid was prepd. by reaction of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid with 2-methylpiperazine dihydrochloride in acetonitrile contg. triethylamine and BF3-THF complex.

RX(4) OF 5 P + Q ===> R



P Q (4)



R

YIELD 92%

RX(4) RCT P 100986-89-8, Q 34352-59-5

STAGE(1)
RGT D 109-63-7 BF3-Et2O, E 121-44-8 Et3N
SOL 75-05-8 MeCN
CON SUBSTAGE(1) 1 hour, room temperature
SUBSTAGE(2) 24 hours, room temperature

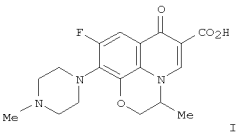
STAGE(2)
RGT G 1310-73-2 NaOH
SOL 7732-18-5 Water
CON 16 hours, pH 8

PRO R 100986-85-4
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 148:403253 CASREACT
TITLE: Preparation of ofloxacin
INVENTOR(S): Muddasani, Pulla Reddy; Peddi, Rajasekhara Reddy; Nannapaneni, Venkaiah Chowdary
PATENT ASSIGNEE(S): Natco Pharma Ltd., India
SOURCE: Indian Pat. Appl., 26pp.
CODEN: INXXBQ
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2003CH01081	A	20070406	IN 2003-CH1081	20031231

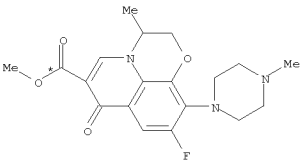
PRIORITY APPLN. INFO.: IN 2003-CH1081 20031231
GI



I

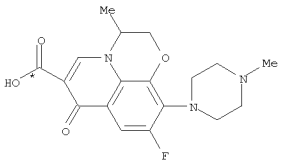
AB A process for the preparation of title compound I was disclosed. For example, ofloxacin I was prepared from 2,4-dichloro-5-fluoro-3-nitrobenzoyl chloride in 6-steps and >60% yield. Of note, the disclosed process can be carried out continuously without the isolation of intermediates.

RX(6) OF 21 ...P ===> S



P (6)

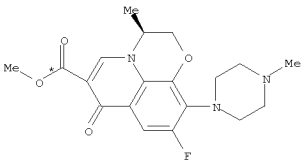
L3 ANSWER 2 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



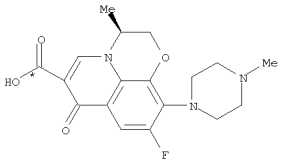
S

RX(6) RCT P 108224-82-4
RGT T 1310-73-2 NaOH
PRO S 82419-36-1
SOL 7732-18-5 Water
CON SUBSTAGE(1) room temperature -> 80 deg C
SUBSTAGE(2) 30 minutes, 70 - 80 deg C

L3 ANSWER 3 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



O



R

RX(6) RCT O 862690-19-5
RGT S 1310-73-2 NaOH
PRO R 100986-85-4
SOL 7732-18-5 Water
CON SUBSTAGE(1) room temperature -> 80 deg C
SUBSTAGE(2) 30 minutes, 70 - 80 deg C

L3 ANSWER 3 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 148:403251 CASREACT
TITLE: Preparation of levofloxacin
INVENTOR(S): Muddasani, Pullareddy; Peddi, Rajasekhara Reddi; Nannapaneni, Venkaiah Chowdary
PATENT ASSIGNEE(S): Natco Pharma Limited, India
SOURCE: Indian Pat. Appl., 22pp.
CODEN: INXXBQ
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 2005CH00305	A	20070316	IN 2005-CH305	20050323

PRIORITY APPLN. INFO.: IN 2005-CH305 20050323
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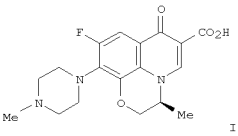


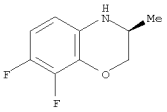
I

AB A process for the preparation of title compound I was disclosed. For example,
levofloxacin I was prepared from 2,4-dichloro-5-fluoro-3-nitrobenzoyl chloride in 6-steps and >60% yield. Of note, the disclosed process can be
carried out continuously without the isolation of intermediates.

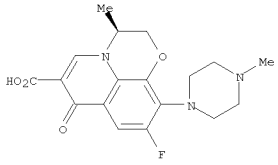
RX(6) OF 21 ...O ===> R

L3 ANSWER 4 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 147:406765 CASREACT
TITLE: Enantiopure 1,4-Benzoxazines via 1,2-Cyclic Sulfamidates. Synthesis of Levofloxacin
AUTHOR(S): Bower, John F.; Szeto, Peter; Gallagher, Timothy
CORPORATE SOURCE: School of Chemistry, University of Bristol, Bristol, BS8 1TS, UK
SOURCE: Organic Letters (2007), 9(17), 3283-3286
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 1,2-Cyclic sulfamidates undergo efficient and regiospecific nucleophilic cleavage with 2-bromophenols and related anilines and thiophenols, followed by Pd(0)-mediated amination to provide substituted and enantiomerically pure 1,4-benzoxazines, quinoxalines and 1,4-benzothiazines. This chemical provides a short and efficient entry to
(3S)-3-methyl-1,4-benzoxazine, a late stage intermediate in the synthesis of levofloxacin.

RX(29) OF 68 ...BM ===> BN



BM

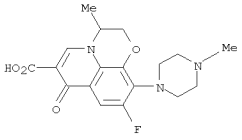


BN

RX(29) RCT BM 106939-42-8
PRO BN 100986-85-4
NTE literature preparation
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

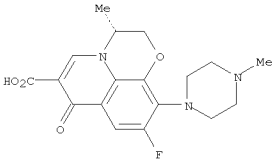
L3 ANSWER 5 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 145:515862 CASREACT
TITLE: 6-O-(hydroxypropyltrimethylammonia)-β-cyclodextrin with low degree of substitution: convenient preparation and its application as a chiral selector in capillary electrophoresis
AUTHOR(S): Zhao, Ming Gang; Hao, Ai You; Li, Jian; Lin, Xiu-Li
CORPORATE SOURCE: School of Chemistry and Chemical Engineering, Shandong University, Jinan, 250100, Peop. Rep. China
SOURCE: Chinese Chemical Letters (2006), 17(3), 407-410
CODEN: CCLEE7; ISSN: 1001-8417
PUBLISHER: Chinese Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A cationic cyclodextrin derivative 6-O-(hydroxypropyltrimethylammonia)-β-cyclodextrin (GTA-β-CD) with low degree of substitution was prepared through a convenient method in solid phase. The product could be used as a valuable chiral selector in the capillary electrophoresis (CE) separation of some acidic drug enantiomers such as naproxen, ofloxacin, ibuprofen and warfarin.

RX(3) OF 5 2 I ===> J + K

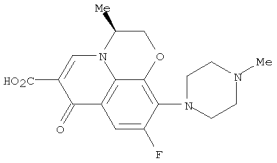


2 I (3) →

L3 ANSWER 5 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



J



K

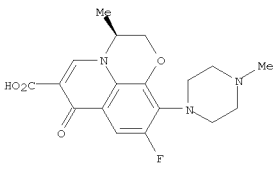
RX(3) RCT I 82419-36-1
PRO J 100986-86-5, K 100986-85-4
CAT 7585-39-9D beta-Cyclodextrin
SOL 7732-18-5 Water
CON 25 deg C, pH 5
NTE stereoselective, buffered solution (phosphate) used, capillary electrophoresis used
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 145:419174 CASREACT
TITLE: Preparation of the levofloxacin hemihydrate
INVENTOR(S): Tanba, Hiroyuki; Imai, Eiji
PATENT ASSIGNEE(S): Shiono Chemical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2006273718	A	20061012	JP 2005-90485	20050328

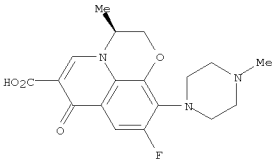
PRIORITY APPLN. INFO.: JP 2005-90485 20050328
AB Levofloxacin hemihydrate (I hemihydrate), useful as bactericide, is prepared by recrystn. of crude I from lower alcs. or ketones having water content ≥0.14 volume% and <4 volume%, or from lower alcs. or ketones containing 1-5 volume% concentrate aqueous NH3. Thus, 10 g crude I was dissolved in 65 mL mixture of EtOH (water content 0.14 volume%) and 2 volume% water at 77.3°, and cooled to room temperature to give 9.51 g I hemihydrate.

RX(1) OF 3 A ===> B



A (1) →

L3 ANSWER 6 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



●1/2 H_2O

B

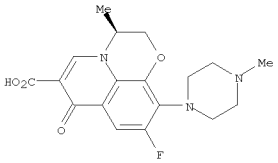
RX(1) RCT A 100986-85-4
PRO B 138199-71-0
SOL 64-17-5 EtOH, 7732-18-5 Water
CON SUBSTAGE(1) 77.3 deg C
SUBSTAGE(2) 77.3 deg C -> room temperature

L3 ANSWER 7 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 145:28013 CASREACT
TITLE: preparation of levofloxacin aspartate
INVENTOR(S): Zhang, Da
PATENT ASSIGNEE(S): He, Yan, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 3 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

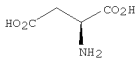
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1718579	A	20060111	CN 2004-10020916	20040707

PRIORITY APPLN. INFO.: CN 2004-10020916 20040707
AB The preparation method comprises reacting levofloxacin with aspartic acid at
20°C for 4 h, at 35°C for 1 h , and at 40°C for 1 h,
adjusting pH to 4.5, performing suction filtration of the white precipitate, and
recrystg. to obtain levofloxacin aspartate with high purity (over 99%).

RX(1) OF 1 A + B ===> C

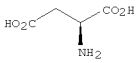


A



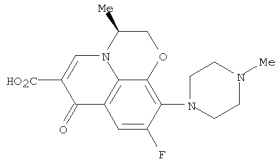
B

(1) →



C: CM 1

L3 ANSWER 7 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



C: CM 2

RX(1) RCT A 100986-85-4, B 56-84-8

STAGE(1)
CON SUBSTAGE(1) 4 hours, 20 deg C
SUBSTAGE(2) 20 deg C -> 35 deg C
SUBSTAGE(3) 1 hour, 35 deg C
SUBSTAGE(4) 35 deg C -> 40 deg C
SUBSTAGE(5) 1 hour, 40 deg C

STAGE(2)
RGT D 12408-02-5 H+
SOL 7732-18-5 Water
CON pH 4.5

PRO C 888969-88-8
NTE unspecified reagent used to adjust pH in final stage

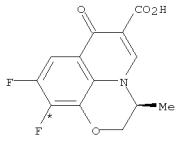
L3 ANSWER 8 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 144:468205 CASREACT
TITLE: Synthetic process for the preparation of levofloxacin hemihydrate from levofloxacin
INVENTOR(S): Rao, Davuluri Rammohan; Dwivedi, Shriprakash Dhar; Sreenivasulu, Pamujula; Sahu, Arabinda; Trinadhachari,
Ganala Naga; Kiran, Surapaneni Sasi
PATENT ASSIGNEE(S): Neuland Laboratories Ltd., India
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006048889	A1	20060511	WO 2004-IN343	20041108
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20070244318	A1	20071018	US 2004-578078	20040811
EP 1809637	A1	20070725	EP 2004-806742	20041108
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				

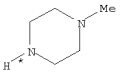
PRIORITY APPLN. INFO.: WO 2004-IN343 20041108
AB A process for preparation of Levofloxacin hemihydrate, having single individual
impurity not more than 0.1% and free from particulate matter and from the other enantiomer (R-form), is described which comprises: dissolving
levofloxacin tech. grade in an aqueous alkaline solution; treating the solution with
activated carbon at room temperature; removing the undissolved particulate
matter by filtration; bringing the pH of the aqueous alkaline levofloxacin solution
to neutral using dilute mineral acid; removing the precipitated particulate matter
by filtration; acidifying the resulting solution; treating the acidified
solution with activated carbon at room temperature; filtering the undissolved
particulate matter by filtration; neutralizing the acidic solution; filtering
again to remove any particulate matter present; and extracting the resulting
product with a chlorinated solvent (e.g., Cl2CH2) and concentrating under vacuum
using aqueous THF or an admixt. with other organic solvents to get highly pure
levofloxacin hemihydrate having a single individual impurity which is

L3 ANSWER 8 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)
<0.1% and is fee from particulate matter and from the other enantiomer (R-form).

RX(8) OF 36 ...W + Z ===> AA

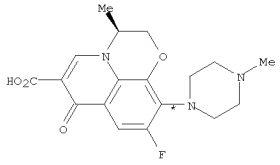


W



Z

(8) →



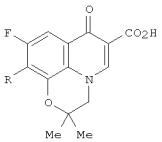
AA

RX(8) RCT W 100986-89-8, Z 109-01-3
RGT AB 110-86-1 Pyridine
PRO AA 100986-85-4
SOL 110-86-1 Pyridine
CON 10 hours, room temperature -> 120 deg C
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

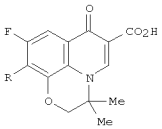
L3 ANSWER 9 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 144:450716 CASREACT
TITLE: Fluorine quinolone compounds and synthetic method thereof
INVENTOR(S): Guo, Qingchun; Wang, Jianming; Liu, Haoru
PATENT ASSIGNEE(S): Beijing Double-Crane Pharmaceutical Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 10 pp. CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1566117	A	20050119	CN 2003-137652	20030619

PRIORITY APPLN. INFO.: CN 2003-137652 20030619
OTHER SOURCE(S): MARPAT 144:450716
GI



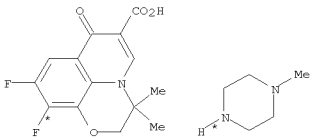
I



II

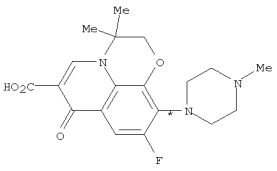
AB Fluorine-containing quinolone derivs. I and II are prepared (where R is halogen, or piperazine, piperidine, or 3-aminopyrrolidine derivative).

RX(15) OF 85 ...AE + AF ===> AS



AE AF

L3 ANSWER 9 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



AS
YIELD 79%

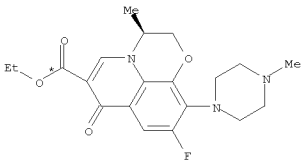
RX(15) RCT AE 107358-79-2, AF 109-01-3
PRO AS 107359-24-0
SOL 67-68-5 DMSO
CON SUBSTAGE(1) 15 minutes, 90 deg C
SUBSTAGE(2) 2.5 hours, 90 deg C
SUBSTAGE(3) overnight, room temperature

L3 ANSWER 10 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 144:370102 CASREACT
TITLE: Preparation of levofloxacin and ofloxacin
INVENTOR(S): Zhang, Weidong; Yang, Zhuhong; Pan, Yibin
PATENT ASSIGNEE(S): Zhejiang Medicine Co., Ltd. Xinchang Pharmaceutical Factory, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 10 pp. CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1594320	A	20050316	CN 2004-10155139	20040622
CN 100412075	C	20080820		

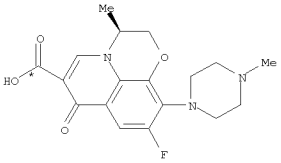
PRIORITY APPLN. INFO.: CN 2004-10155139 20040622
AB Levofloxacin and ofloxacin are prepared by charging solution into Et 2-(2,3,4,5-tetrafluorobenzoyl-3-ethoxy)acrylate crude product, freezing, adding L-2-aminopropanol or 2-aminopropanol, thermal insulating till the completion of conversion, alkalizing, heating at 50-90°, charging N-Me piperazine into mother liquor, stirring for 1-3 h at 55-95°, decompressing and reclaiming N-methylpiperazine, thermal insulating, plunging reaction liquor into water, agitating, cooling down and filtering, charging water and acid into filtrate, stirring till the completion of hydrolysis, adjusting the pH to 7.0 with alkali liquor, extracting and concentrating the extract layer.

RX(2) OF 6 ...D ===> H



D

L3 ANSWER 10 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



H
YIELD 94%

RX(2) RCT D 177472-30-9

STAGE(1)
RGT I 7647-01-0 HCl
SOL 7732-18-5 Water
CON 0.5 hours, reflux

STAGE(2)
RGT J 1310-73-2 NaOH
SOL 7732-18-5 Water
CON pH 7

PRO H 100986-85-4
NTE yield depends on reaction conditions

L3 ANSWER 11 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 144:312117 CASREACT
TITLE: Process for preparation of levofloxacin hemihydrate by adjusting the moisture content of the solvent to 12-20% during crystallization.
INVENTOR(S): Chava, Satyanaryana; Gorantla, Seeta Ramanjaneyulu; Gogulapathi, Venkata Panakala Rao
PATENT ASSIGNEE(S): Matrix Laboratories Ltd, India
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

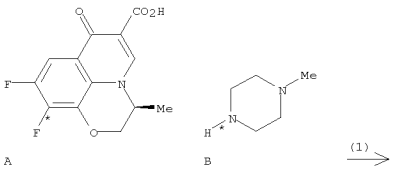
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006030452	A1	20060323	WO 2005-IN264	20050808
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
IN 2004CH00931	A	20060616	IN 2004-CH931	20040917
EP 1797101	A1	20070620	EP 2005-788709	20050808
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
US 20080097095	A1	20080424	US 2007-662945	20070403

PRIORITY APPLN. INFO.: IN 2004-CH931 20040917
WO 2005-IN264 20050808

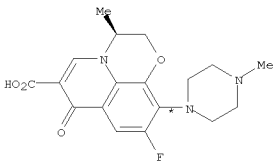
AB Levofloxacin hemihydrate was prepared by reaction of (S)-9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with N-methylpiperazine in a polar solvent at 120-125°, removal of BuOH at <100°, dissolving the residue in PhMe/CHCl3 and removing insolubles, removing solvent and adding isopropanol, cooling and isolating crude levofloxacin, dissolving the crude levofloxacin in PhMe/CHCl3, removing insolubles, removing the PhMe/CHCl3 mixture, adding isopropanol, adding a known quantity of H2O and mixing for 5-30 min., cooling to 15-35°, and isolating and drying the product.

RX(1) OF 1 A + B ===> C

L3 ANSWER 11 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



A B (1)



●1/2 H_2O

C

RX(1) RCT A 100986-89-8, B 109-01-3
PRO C 138199-71-0
SOL 71-36-3 BuOH
CON SUBSTAGE(1) room temperature -> 125 deg C
SUBSTAGE(2) 6 hours, 120 - 125 deg C
NTE workup
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 144:51612 CASREACT
TITLE: Methods for preparation of Levofloxacin and Floxacin
INVENTOR(S): Ye, Weidong; Zhang, Weidong; Yang, Zhuhong
PATENT ASSIGNEE(S): Zhe Jiang Medicine Co., Ltd. Xinchang Pharmaceutical Factory, Peop. Rep. China
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

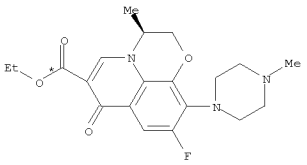
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005123746	A1	20051229	WO 2004-CN954	20040816
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: WO 2004-CN954 20040816

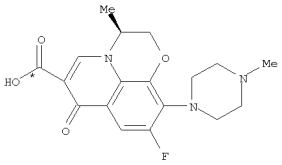
AB The invention relates to the methods for the preparation of anti-infective agents, Levofloxacin and Floxacin. Title compds. were synthesized from tetrafluorobenzoic acid via ethyl-2-(2,3,4,5-tetrafluorobenzoyl)-3-ethoxyacrylate reacted with L-aminopropanol or DL-aminopropanol and cyclization with N-methylpiperazine, further hydrolysis to provide the corresponding title products. Thus, ethyl-2-(2,3,4,5-tetrafluorobenzoyl)-3-ethoxyacrylate dissolved in DMF and cooled the temperature to 0°, dropwise added L-aminopropanol and reacted for 0.5 h, then mixed with potassium carbonate reacted at 70-80° for 3 h, after that, adding N-methylpiperazine to the mother liquid further reacted at 60-70° for 2 h then evaporated the excess N-methylpiperazine and quenched the reaction in water to give white solid, finally hydrolysis with concentrated hydrochloric acid to provide Levofloxacin.

RX(2) OF 6 ...D ===> G

L3 ANSWER 12 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



D (2)



G
YIELD 94%

RX(2) RCT D 177472-30-9

STAGE(1)
RGT H 7647-01-0 HCl
SOL 7732-18-5 Water
CON 30 minutes, reflux

STAGE(2)
RGT I 1310-73-2 NaOH
SOL 7732-18-5 Water
CON pH 7

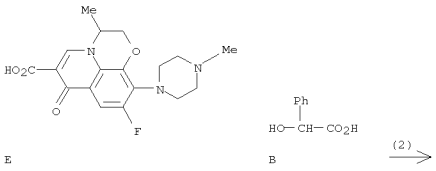
PRO G 100986-85-4
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 143:172901 CASREACT
TITLE: Ciprofloxacin mandelate, ofloxacin mandelate and their preparation
INVENTOR(S): Li, Shengzheng; Wang, Yuncai
PATENT ASSIGNEE(S): Xi'an Jiaotong University, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 11 pp. CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1418875	A	20030521	CN 2002-139499	20021101
CN 1199951	C	20050504		
PRIORITY APPLN. INFO.:			CN 2002-139499	20021101

AB The invention discloses a method for preparing ciprofloxacin and ofloxacin mandelates by reacting mandelic acid with the corresponding free base (at the molar ratio of 1.5-2.0:1) in ethanol under refluxing for 4 h; adjusting to pH 6-7, filtering under heating, crystallizing at room temperature for 12 h then at 0-5° for 12 h, and drying at room temperature for 6 h, then at 120° for 2 h. Both mandelic salts may be decomposed in a medium of pH 4.6-4.8.

RX(2) OF 2 E + B ===> F



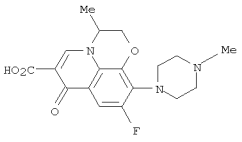
E

B

(2)

L3 ANSWER 13 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)

F: CM 1



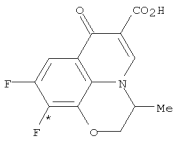
F: CM 2

RX(2) RCT E 82419-36-1, B 90-64-2
PRO F 860813-31-6
SOL 64-17-5 EtOH
CON 4 hours, reflux, pH 6 - 7

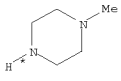
L3 ANSWER 14 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 141:295973 CASREACT
TITLE: Modified route for synthesis of Ofloxacin
AUTHOR(S): Wang, Xundao; Tan, Lingyan; Wang, Bin
CORPORATE SOURCE: College of Chemical Engineering, Zhengzhou University, Zhengzhou, 450002, Peop. Rep. China
SOURCE: Zhongguo Kangshengsu Zazhi (2003), 28(6), 341-343 CODEN: ZKZAEY; ISSN: 1001-8689
PUBLISHER: Zhongguo Kangshengsu Zazhishe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Title compound was prepared from 2,3,4-trifluoronitrobenzene via aromatic substitution with 2-hydroxymethyl-2-methyl-1,3-dioxolane, then hydrolysis to obtain 2-acetonyloxo-3,4-difluoronitrobenzene, after hydrogenation and cyclization in the presence of Raney Ni to obtain 7,8-difluoro-2,3-dihydro-3-methyl-4H-1,4-benzoxazine, further substitution with di-Et ethoxymethylenemalonate (EMME) and cyclization in the presence of concentrated H2SO4/acetic anhydride, hydrolyzation with HCl/HOAc in water under refluxing to obtain 9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid, finally substitution with N-methylpiperazine in DMSO, giving the product with overall yield 57%.

RX(1) OF 10 ...A + B ===> C



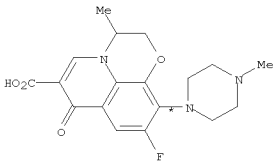
A



B

(1)

L3 ANSWER 14 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



C
YIELD 85%

RX(1) RCT A 82419-35-0, B 109-01-3

STAGE(1)
RGT D 121-44-8 Et3N
SOL 67-68-5 DMSO
CON 8 hours, 80 - 85 deg C

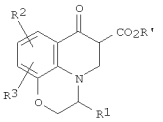
STAGE(2)
RGT E 7647-01-0 HCl, F 7440-44-0 Carbon
SOL 7732-18-5 Water
CON 1 hour, 60 - 70 deg C, pH 1

PRO C 82419-36-1

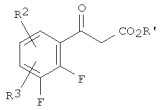
L3 ANSWER 15 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 140:287413 CASREACT
TITLE: Preparation of optically active tricyclic compounds without forming diastereomers
INVENTOR(S): Tanba, Hiroyuki; Imai, Eiji; Mao, Shun-Cong
PATENT ASSIGNEE(S): Shiono Chemical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004099494	A	20040402	JP 2002-262283	20020909

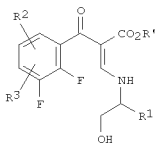
PRIORITY APPLN. INFO.: JP 2002-262283 20020909
OTHER SOURCE(S): MARPAT 140:287413
GI



I



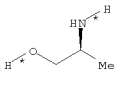
II



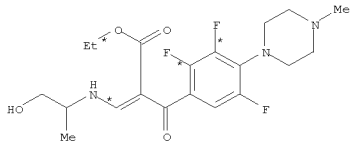
III

AB Title tricyclic compds. I (R1 = lower alkyl; R2 = H, halo; R3 = halo, substituted amino, N-containing heterocyclyl; R' = H, lower alkyl), which are known to be useful as antibacterial agents, are prepared by treatment of benzoylacetate esters II (R2, R3, R' = same as above) with Me2NCH(OMe)2 and optically active H2NCHR1CH2OH (R1 = same as above), followed by cyclization of the resulting optically active products III (R1-R3, R' = same as above). Thus, II (R2 = 4-F, R3 = 5-F, R' = 4-methyl-1-piperazinyl) was condensed with Me2NCH(OMe)2 and (S)-2-aminopropanol, treated with FK in DMF, treated with NaH in dioxane, and hydrolyzed to give levofloxacin.

RX(3) OF 6 ...F + H ===> K

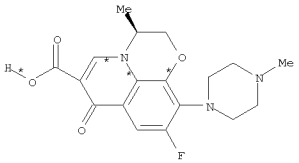


F



H

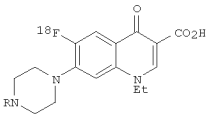
(3)



K

RX(3) RCT F 2749-11-3, H 113933-53-2
RGT L 7789-23-3 KF
PRO K 100986-85-4
SOL 68-12-2 DMF
CON 3 hours, 140 - 165 deg C

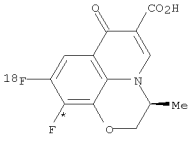
L3 ANSWER 16 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 140:59503 CASREACT
TITLE: A general method for the fluorine-18 labeling of fluoroquinolone antibiotics
AUTHOR(S): Langer, Oliver; Mitterhauser, Markus; Wadsak, Wolfgang; Brunner, Martin; Mueller, Ulrich; Kletter, Kurt; Mueller, Markus
CORPORATE SOURCE: Division of Clinical Pharmacokinetics, Department of Clinical Pharmacology, Austria
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (2003), 46(8), 715-727
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



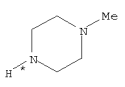
I

AB [18F]norfloxacin (I, R = H) and [18F]pefloxacin (I, R = Me) were prepared The radiosynthesis consisted of 18F/19F exchange on a 7-chloro-substituted precursor mol., followed by coupling reactions with piperazine or 1-methylpiperazine. Starting from 51-58 GBq of [18F]fluoride 1.9-2.0 GBq of [18F]norfloxacin or [18F]pefloxacin, ready for i.v. injection, could be obtained in a synthesis time of 130 min (3.5-3.8% overall radiochem. yield). The preparation of [18F]levofloxacin was attempted but failed to afford the product in practical amts.

RX(5) OF 11 ...J + Q ===> R



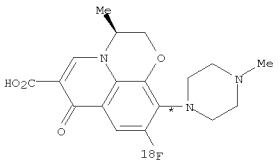
J



Q

(5)

L3 ANSWER 16 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



R

RX(5) RCT J 637328-07-5

STAGE(1)
RGT O 121-43-7 Me borate, P 64-19-7 AcOH
SOL 67-68-5 DMSO
CON SUBSTAGE(1) 1 minute
SUBSTAGE(3) 2 minutes, room temperature

STAGE(2)
RCT Q 109-01-3
SOL 67-68-5 DMSO
CON SUBSTAGE(2) 40 minutes, 180 deg C

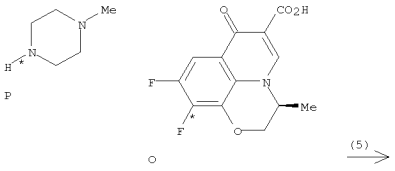
PRO R 637328-10-0
NTE thermal
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 139:197504 CASREACT
TITLE: Preparation of levofloxacin
INVENTOR(S): Wang, Jiesheng; Wang, Bin
PATENT ASSIGNEE(S): Kunshan Shuanghe Pharmaceuticals Co., Ltd., Peop. Rep.
China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 7 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1357548	A	20020710	CN 2001-134025	20010929
CN 1157396	C	20040714		

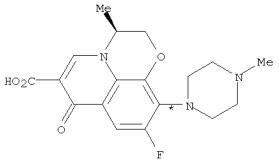
PRIORITY APPLN. INFO.: CN 2001-134025 20010929
AB The process comprises substituting 2,4,5-trifluoro-3-nitrobenzoyl fluoride with Cl2 at 190-195° for 16-18 h to obtain 3-chloro-2,4,5-trifluorobenzoyl fluoride, substituting with (chloromagnesio)malonic acid Et ester K salt at 20-25° for 8-10 h, decarboxylating with 6-8% HCl, extracting with Et acetate to obtain 3-(3-chloro-2,4,5-trifluorophenyl)-3-oxopropanoic acid Et ester; etherifying with tri-Et orthoformate, aminating with 3-amino-1-propanol at 10-15° for 3-4 h, cyclizing to obtain 9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid Et ester; hydrolyzing, and substituting with 1-methylpiperazine in pyridine.

RX(5) OF 15 ...P + O ===> Q



P O (5)

L3 ANSWER 17 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



Q

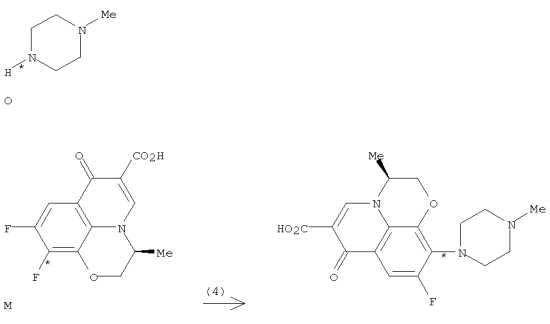
RX(5) RCT P 109-01-3, O 100986-89-8
PRO Q 100986-85-4
SOL 110-86-1 Pyridine
CON 6 hours, reflux

L3 ANSWER 18 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 139:197503 CASREACT
TITLE: Preparation of levofloxacin
INVENTOR(S): Wang, Bin; Wang, Jiesheng
PATENT ASSIGNEE(S): Kunshan Shuanghe Pharmaceuticals Co., Ltd., Peop. Rep.
China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 5 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1357547	A	20020710	CN 2001-134024	20010929
CN 1170830	C	20041013		

PRIORITY APPLN. INFO.: CN 2001-134024 20010929
AB The process comprises substituting 2,4,5-trifluoro-3-chlorobenzoyl fluoride with (chloromagnesio)malonic acid Et ester K salt at 20-25° for 8-10 h, decarboxylating with 6-8% HCl, extracting with Et acetate to obtain 3-(3-chloro-2,4,5-trifluorophenyl)-3-oxopropanoic acid Et ester; etherifying with tri-Et orthoformate, aminating with 3-amino-1-propanol at 10-15° for 3-4 h, cyclizing to obtain 9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid Et ester; hydrolyzing, and substituting with 1-methylpiperazine in pyridine.

RX(4) OF 10 ...O + M ===> P



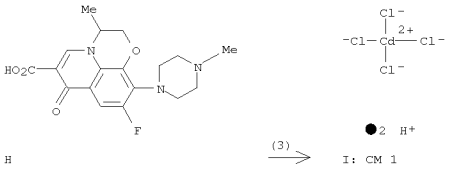
O M (4) P

RX(4) RCT O 109-01-3, M 100986-89-8

L3 ANSWER 18 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)
PRO P 100986-85-4
SOL 110-86-1 Pyridine
CON 6 hours, reflux

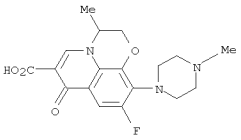
L3 ANSWER 19 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 138:197695 CASREACT
TITLE: Structure and antimicrobial activity of some new norfloxacin and ofloxacin divalent metal ion complexes
AUTHOR(S): Uivarosi, Valentina; Neagoe, S.; Aldea, Victoria; Nitulescu, Andreea
CORPORATE SOURCE: Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Rom.
SOURCE: Romanian Archives of Microbiology and Immunology (2001), 60(3), 267-277
CODEN: RAMIE5; ISSN: 1222-3891
PUBLISHER: Institutul Cantacuzino
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Studies of some new complexes of norfloxacin (Nf) and ofloxacin (Of) with Cd(II) and Hg(II) are presented. The synthesis, purification and the elemental chemical anal. of the Nf and Of compds. have been performed in order to obtain the chemical formulas. These formulas are confirmed by mol. mass detns. IR, UV-VIS reflectance spectra were recorded, as well as elec. conductometric measurements. The obtained compds. are electrolytes. The antimicrobial activity was tested using plates containing Muller-Hinton cultures as well as Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa. Nf, Of and the products here exert an obvious antimicrobial activity and these are compared to that of Zn Nf and Of complexes.

RX(3) OF 4 H ===> I



H I: CM 1

L3 ANSWER 19 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



I: CM 2

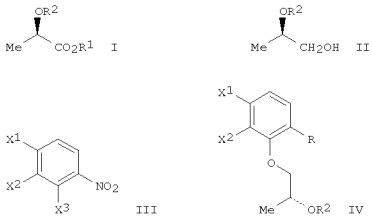
RX(3) RCT H 82419-36-1
RGT C 7647-01-0 HCl, D 10108-64-2 CdCl2
PRO I 498563-89-6
SOL 7732-18-5 Water
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 137:232675 CASREACT
TITLE: Process for preparation of optically active 2-hydroxypropoxyaniline derivatives as intermediates for levofloxacin via enzymic or microbial stereoselective hydrolysis of racemic lactic acid ester
INVENTOR(S): Sato, Kouji; Yagi, Tsutomu; Kubota, Kazuo; Imura, Akihiro
PATENT ASSIGNEE(S): Daiichi Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002070726	A1	20020912	WO 2002-JP2054	20020306
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2440411	A1	20020912	CA 2002-2440411	20020306
AU 2002236224	A1	20020919	AU 2002-236224	20020306
EP 1367132	A1	20031203	EP 2002-702751	20020306
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CN 1496409	A	20040512	CN 2002-806097	20020306
JP 4169332	B2	20081022	JP 2002-570748	20020306
NO 2003003880	A	20030902	NO 2003-3880	20030902
KR 868619	B1	20081113	KR 2003-711568	20030903
US 20040077060	A1	20040422	US 2003-469827	20030905
US 7217560	B2	20070515		
PRIORITY APPLN. INFO.:			JP 2001-63945	20010307
			WO 2002-JP2054	20020306

OTHER SOURCE(S): MARPAT 137:232675
GI

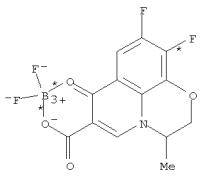
L3 ANSWER 20 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



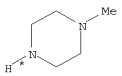
AB Treatment of a racemic lactate derivative of formula MeCH(OR2)CO2R1 (R1 = C1-6 alkyl; R2 = hydroxy-protecting group) with an enzyme having an ability to hydrolyze an ester asym. causes specific hydrolysis of the ester moiety of one of the optical isomers constituting the racemic lactate derivative to give optically active lactic acid esters (I; R1, R2 = same as above). The alkyl lactate I is reduced by metal borohydride in the presence of a primary alc. in nonalcoholic solvent to optically active 2-hydroxypropanol (II; R2 = same as above) which is condensed with trihalonitrobenzene (III; X1-X3 = halo) in the presence of a base to give 3,4-dihalo-2-(2-hydroxypropoxy)nitrobenzene derivative (IV; R = NO2; R2, X1, X2 = same as above). Simultaneous conversion of the nitro group into the amino group and cleavage of the protecting group gives 3,4-dihalo-2-(2-hydroxypropoxy)aniline IV (R = NH2, R2 = H; X1, X2 = same as above) which is converted into levofloxacin (antibacterial) in several steps. Thus, 300 mg 2-benzyloxypropionic acid Et ester was suspended in 0.1 M phosphate buffer (pH 6.5) and treated with 6 mg lipase (Biochem. Industry Co.) at 30° for 24 h to give 102 mg (R)-2-benzyloxypropionic acid Et ester (98.8% ee) which (100 mg) was reduced by NaBH4 in 0.15 mL MeOH and 0.8 mL toluene at 40° for 3 h to give 79 mg (R)-2-benzyloxy-1-propanol (V) (99% ee). A solution of 4.0 g V and 4.13 g 2,3,4-trifluoronitrobenzene in 40 mL toluene was added to a suspension of 5.40 g KOH and 3.33 g K2CO3 in 180 mL toluene under ice-cooling and stirred at the same temperature for 1 h to give 7.55 g (R)-3,4-difluoro-2-(2-benzyloxypropoxy)nitrobenzene which (1.0 g) was hydrogenated over 1.0 g 7.5% Pd/C in 10 ethanol under hydrogen atmospheric for 6 h to give 600 mg (R)-3,4-difluoro-2-(2-hydroxypropoxy)aniline (99.0% ee).

RX(9) OF 45 ...Y + AB ===> AC

L3 ANSWER 20 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)

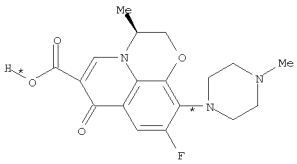


Y



AB

(9)



AC

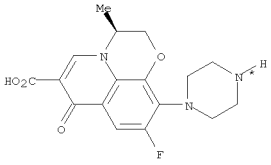
RX(9) RCT Y 113348-94-0, AB 109-01-3
PRO AC 100986-85-4
SOL 67-68-5 DMSO
NTE amination at room temp. for 17 h
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L3 ANSWER 21 OF 45 CASREACT COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 136:232258 CASREACT
TITLE: Synthesis of [11C]levofloxacin
AUTHOR(S): Berridge, M. S.; Burnazi, E. M.
CORPORATE SOURCE: Department of Radiology, Case Western Reserve University Medical School, Cleveland, OH, 44106, USA
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (2001), 44(12), 859-864
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Levofloxacin, the pure S enantiomer of the fluoroquinolone antibiotic ofloxacin, was labeled via methylation of des-methyllevofloxacin with [11C]methyl iodide. The methylation reaction was regioselective, giving predominantly the preferred methylamine at high temperature in DMF, while otherwise giving predominantly the Me ester of des-methyllevofloxacin. Labeled levofloxacin was obtained in 80% chemical yield after a 45 min synthesis.

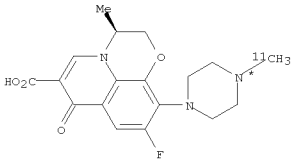
RX(1) OF 3 A + B ===> C



A

B

(1)



C

L3 ANSWER 21 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)

RX(1) RCT A 117707-40-1

STAGE(1)
RGT D 1310-73-2 NaOH
SOL 68-12-2 DMF

STAGE(2)
RCT B 54245-42-0

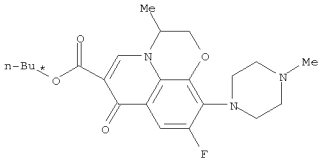
PRO C 403655-77-6
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L3 ANSWER 22 OF 45 CASREACT COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 135:317507 CASREACT
TITLE: Enantioselective production of levofloxacin by immobilized porcine liver esterase
AUTHOR(S): Lee, Sang-Yoon; Min, Byung-Hyuk; Hwang, Sung-Ho; Koo, Yoon-Mo; Lee, Choul-Kyun; Song, Seong-Won; Oh, Sun-Young; Lim, Sang-Min; Kim, Sang-Lin; Kim, Dong-Il
CORPORATE SOURCE: Department of Biological Engineering, Inha University, Incheon, 402-751, S. Korea
SOURCE: Biotechnology Letters (2001), 23(13), 1033-1037
CODEN: BILED3; ISSN: 0141-5492
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Porcine liver esterase, which cleaves ofloxacin Bu ester enantioselectively to levofloxacin, was successfully immobilized in calcium alginate and polyacrylamide gel. Immobilized esterase in 5% (w/v) calcium alginate exhibited 58% immobilization efficiency and could be reused five times without severe loss of enzyme activity. On the other hand, entrapped esterase in polyacrylamide gel, composed of 20% of total monomer and 8.3% of crosslinking agent, could be reused 10 times, and 51% of enzyme activity remained after the 10th batch without decrease of enantioselectivity. Compared with entrapped methods, significant reduction of enzyme activity was found in the case of phys. adsorption on to QAE-Sephadex.

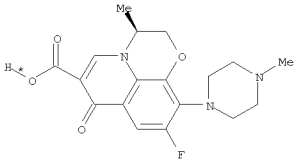
RX(1) OF 1 A ===> B



A

(1)

L3 ANSWER 22 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



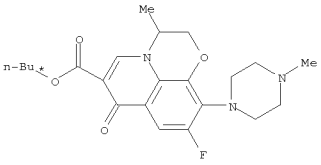
B

RX(1) RCT A 358632-22-1
PRO B 100986-85-4
CAT 9016-18-6 Carbonic esterase
SOL 7732-18-5 Water
NTE Biotransformation, stereoselective, Porcine liver esterase used as catalyst, enzymic, enzyme immobilized in calcium alginate or polyacrylamide gel, buffered soln.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 45 CASREACT COPYRIGHT 2009 ACS on STN

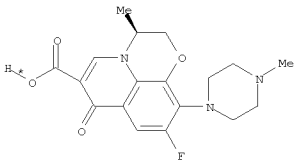
ACCESSION NUMBER: 135:209933 CASREACT
TITLE: Polyacrylamide gel immobilization of porcine liver esterase for the enantioselective production of levofloxacin
AUTHOR(S): Lee, Sang-Yoon; Min, Byung-Hyuk; Song, Seong-Won; Oh, Sun-Young; Lim, Sang-Min; Kim, Sang-Lin; Kim, Dong-Il
CORPORATE SOURCE: Department of Biological Engineering and Center for Advanced Bioseparation Technology, Inha University, Incheon, 402-751, S. Korea
SOURCE: Biotechnology and Bioprocess Engineering (2001), 6(3),
179-182
CODEN: BBEIAU; ISSN: 1226-8372
PUBLISHER: Korean Society for Biotechnology and Bioengineering
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Porcine liver esterase was immobilized in polyacrylamide gel for the enantioselective production of levofloxacin from ofloxacin Bu ester. The initial activity of immobilized esterase was found to be significantly affected by the polyacrylamide gel composition The optimum concns. of monomer and crosslinker were determined to be 20% and 8.3%, resp. The activity of immobilized esterase was 55.4% compared to a free enzyme. Enantiomeric excess was maintained at 60%, almost the same level as that of free enzyme. In addition, the immobilized esterase could be used repeatedly up to 10 times without experiencing any severe loss of activity and enantioselectivity.

RX(1) OF 1 A ===> B



A

L3 ANSWER 23 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



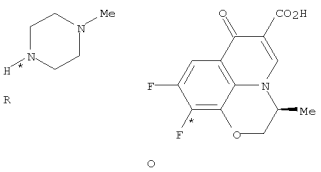
B

RX(1) RCT A 358632-22-1
PRO B 100986-85-4
CAT 9016-18-6 Carbonic esterase
NTE biotransformation, enzymic, phosphate buffer
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

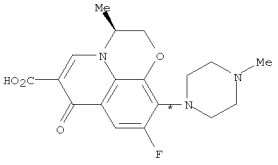
L3 ANSWER 24 OF 45 CASREACT COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 135:107303 CASREACT
TITLE: Studies on stereospecific synthesis of (S)-(-)-ofloxacin
AUTHOR(S): Li, Jiaming; Wang, Gang; Zhang, Xing; Zhou, Sixiang
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, Anhui College of Traditional Chinese Medicines, Hefei, 230038, Peop. Rep. China
SOURCE: Zhongguo Yaowu Huaxue Zazhi (2000), 10(4), 276-278
CODEN: ZYHZEF; ISSN: 1005-0108
PUBLISHER: Zhongguo Yaowu Huaxue Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB (S)-(-)-Ofloxacin was synthesized from 2,3,4,5- tetrafluorobenzoic acid by chlorination, condensation with di-Et malonate, partial hydrolysis, decarboxylation, condensation with tri-Et orthoformate, substitution with (S)-(+)-2-aminopropanol, cyclization, hydrolysis, and substitution with N-methylpiperazine. The overall yield from 2,3,4,5-tetrafluorobenzoic acid was 39.2%.

RX(4) OF 10 ...R + O ===> S



R O



S
YIELD 82%

RX(4) RCT R 109-01-3, O 100986-89-8

L3 ANSWER 24 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)
PRO S 100986-85-4
SOL 67-68-5 DMSO

L3 ANSWER 25 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 134:222719 CASREACT
TITLE: Process for the preparation of benzoxazine derivatives
and intermediates therefor
INVENTOR(S): Sato, Kouji; Takayanagi, Yoshihiro; Okano, Katsuhiko; Nakayama, Keiji; Imura, Akihiro; Itoh, Mikihiro; Yagi,
Tsutomu; Kobayashi, Yukinari; Nagai, Tomoyuki
PATENT ASSIGNEE(S): Daiichi Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001018005	A1	20010315	WO 2000-JP6094	20000907
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2380359	A1	20010315	CA 2000-2380359	20000907
EP 1211254	A1	20020605	EP 2000-957001	20000907
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
CN 1379779	A	20021113	CN 2000-814383	20000907
CN 1195759	C	20050406		
CN 1532181	A	20040929	CN 2004-10032355	20000907
RU 2258069	C2	20050810	RU 2002-105997	20000907
CN 1733744	A	20060215	CN 2005-10097627	20000907
CN 100432060	C	20081112		
CN 101157619	A	20080409	CN 2007-10154339	20000907
JP 2002121179	A	20020423	JP 2000-273449	20000908
TW 254048	B	20060501	TW 2000-89118428	20000908
JP 2001163841	A	20010619	JP 2000-297799	20000929
NO 2002001124	A	20020508	NO 2002-1124	20020306
US 6872823	B1	20050329	US 2002-70556	20020621
US 20050027119	A1	20050203	US 2004-922832	20040823
US 7087778	B2	20060808		
US 20060014947	A1	20060119	US 2005-225058	20050914
US 7189847	B2	20070313		

PRIORITY APPLN. INFO.:
JP 1999-253958 19990908
JP 1999-278019 19990930
JP 2000-239256 20000808
JP 2000-239262 20000808
CN 2000-814383 20000907
CN 2004-10032355 20000907

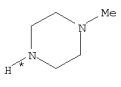
L3 ANSWER 25 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)
WO 2000-JP6094 20000907
US 2002-70566 20020307
US 2002-70556 20020621
US 2004-922832 20040823
OTHER SOURCE(S): MARPAT 134:222719
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

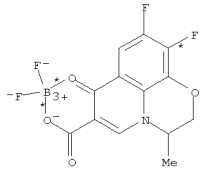
AB The invention provides an industrially advantageous process for the preparation of antimicrobial drugs, specifically (3S)-9-halo-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid (I; X = halo) (e.g. levofloxacin), and industrially advantageous processes for the preparation of intermediates of antimicrobial drugs. The process involves, e.g. cyclization of dialkyl [(3,4-dihydro-2H-1,4-benzoxazin-4-yl)methylene]malonate derivative (II; X1, X2 = halo; R5, R6 = C1-6 alkoxy) by treatment with Et2O.BF3 and (3S)-9,10-dihalo-3-methyl-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid-BF2 complex (III; X1, X2 = same as above) with 4-methylpiperazine. Thus, (2S)-2-(2,3,4-trifluoroanilino)-1-propanol, ethoxymethylenemalonic acid di-Et ester, and tetrahexylammonium chloride were dissolved in acetone, treated with K2CO3, and stirred at room temperature for 4.5 h to give 84% di-Et [2,3,4-trifluoro[(1S)-2-hydroxy-1-methylethyl]anilino]methylenemalonate (IV). A solution of IV in DMF was added dropwise to potassium tert-butoxide in DMF under ice-cooling and stirred at 60° for 18 h to give 79% II (X1 = X2 = F, R6 = Et) which was mixed with Ac2O, treated with Et2O.BF3 at 140°, and stirred at the same temperature for 1 h to give III (X1 = X2 = F). The latter compound was dissolved in DMSO, treated with Et3N and N-methylpiperazine, stirred at room temperature for 17 h, and concentrated in vacuo to dryness, and the residue was washed with Et2O, dissolved in 95% ethanol containing Et3N, refluxed for 8 h, cooled, and evaporated in vacuo to dryness. The residue was dissolved in 5% HCl and extracted with CHCl3, and the aqueous layer was adjusted at pH 11 with 1 M NaOH and then at pH 7.4 with 1 M HCl, and extracted with CHCl3 to give levofloxacin.

RX(4) OF 10 ...M + J ===> N

L3 ANSWER 25 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)

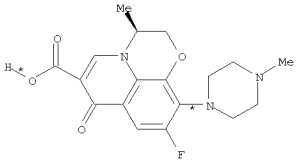


M



J

(4)



N

RX(4) RCT M 109-01-3, J 113348-94-0

STAGE(1)
RGT O 121-44-8 Et3N

STAGE(2)
RGT O 121-44-8 Et3N
SOL 67-56-1 MeOH, 60-29-7 Et2O

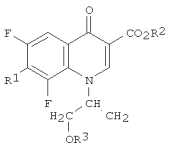
STAGE(3)
RGT P 7647-01-0 HCl
SOL 7732-18-5 Water

PRO N 100986-85-4
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 26 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 134:147504 CASREACT
TITLE: Preparation of quinolinecarboxylic acids and ofloxacin
INVENTOR(S): Nakamura, Hiroshi; Yokota, Shizumasa; Umesawa, Isao; Inoue, Tsutomu
PATENT ASSIGNEE(S): Fuji Yakuhin K. K., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001031654	A	20010206	JP 1999-207750	19990722

PRIORITY APPLN. INFO.: JP 1999-207750 19990722
OTHER SOURCE(S): MARPAT 134:147504
GI

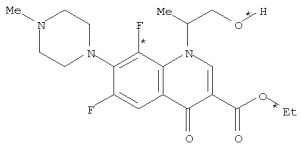


I

AB Title compds. I (R1 = F, 4-methyl-1-piperazinyl; R2 = H, lower alkyl; R3 = primary OH-protecting group) are prepared N-(1-acetoxymethyl)ethyl-N-[2,2-bis(ethoxycarbonyl)]vinyl-2,3,4-trifluoroaniline (2.33 g) was reacted with polyphosphoric acid Et ester at 140° for 5 min to give 1.88 g Et 6,7,8-trifluoro-1,4-dihydro-1-(1-acetoxymethyl)ethyl-4-oxoquinoline-3-carboxylate, which was reacted with 1-methylpiperazine in PhMe at 100° for 2 h and cyclized in the presence of NaOH in 2-propanol at 100° for 2 h to give ofloxacin.

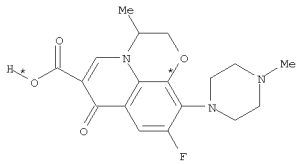
RX(3) OF 6 ...D ===> F

L3 ANSWER 26 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



D

(3)



F

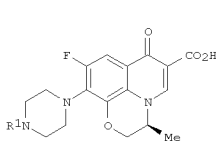
RX(3) RCT D 113933-54-3
RGT G 1310-73-2 NaOH
PRO F 82419-36-1
SOL 67-63-0 Me2CHOH

L3 ANSWER 27 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 133:193174 CASREACT
TITLE: Preparation of (-)-pyridobenzoxazinecarboxylates from (+)-ethyl 2-(4-chloro-5-fluoro-2-halo-3-nitobenzoyl)-3-[(1-hydroxypropy-2(S)-yl)amino]acrylate.
INVENTOR(S): Park, Young-jun; Lee, Ho-seong; Kim, Min-hwan; Kim, Kyung-chul
PATENT ASSIGNEE(S): Samsung Electronics Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

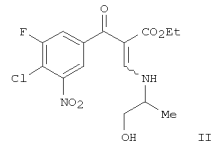
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050428	A1	20000831	WO 2000-KR145	20000223
W: BR, CN, IN, US				
RW: DE, ES, FR, GB, IT				
KR 2000056615	A	20000915	KR 1999-6093	19990224
JP 2000247980	A	20000912	JP 1999-228868	19990812
JP 3530784	B2	20040524		
BR 2000005132	A	20010102	BR 2000-5132	20000223
EP 1073662	A1	20010207	EP 2000-905443	20000223
EP 1073662	B1	20040414		
R: DE, ES, FR, GB, IT				
CN 1125073	C	20031022	CN 2000-800214	20000223
ES 2215024	T3	20041001	ES 2000-905443	20000223
JP 2000299412	A	20001024	JP 2000-47715	20000224
IN 2000KN00414	A	20060127	IN 2000-KN414	20001018
US 6316618	B1	20011113	US 2000-674323	20001024

PRIORITY APPLN. INFO.: KR 1999-6093 19990224
WO 2000-KR145 20000223
OTHER SOURCE(S): MARPAT 133:193174
GI

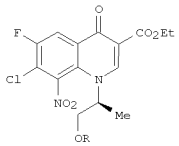
L3 ANSWER 27 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



I



II

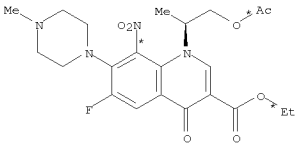


III

AB Title compds. (I; R1 = H, alkyl) were prepared by (1) reaction of aminoacrylates (II; X = halo; R = H) with RaZ [Ra = COR2; R2 = alkyl, alkoxy, cycloalkoxy, (substituted) Ph, etc.; Z = leaving group] or RbNCY [Rb = alkyl, (substituted) Ph] to give II [X = halo; R = COR2, RbNHCY; R2 = alkyl, alkoxy, cycloalkoxy, (substituted) Ph, etc.; Rb = alkyl, (substituted) Ph; Y = O, S], (2) treatment of the latter with base in an organic polar solvent to give III (R as above), (3) treatment of III with (R1-substituted) piperazine in an organic polar solvent in the presence of base, and (4) hydrolysis and cyclization in the presence of metal hydroxide in an organic solvent. Thus, (+)-Et 2-(2,4-dichloro-3-nitro-5-fluorobenzoyl)-3-[(1-hydroxyprop-2(S)-yl)amino]acrylate in ethylene dichloride at -40° was treated with Et3N and AcCl to give 100% (+)-Et 2-(2,4-dichloro-3-nitro-5-fluorobenzoyl)-3-[(1-acetoxypropyl-2(S)-yl)amino]acrylate. The latter was refluxed with K2CO3 in MeCN to give 96% (-)-Et N-(1-acetoxyprop-2(S)-yl)-6-fluoro-7-chloro-8-nitro-4-quinolone-3-carboxylate. This was refluxed with N-methylpiperazine and K2CO3 in MeCN to give 100% (-)-Et N-(1-acetoxyprop-2(S)-yl)-6-fluoro-7-(N-methylpiperazinyl)-8-nitro-4-quinolone-3-carboxylate. The latter was refluxed with KOH in EtOH to give 57% I (R1 = Me).

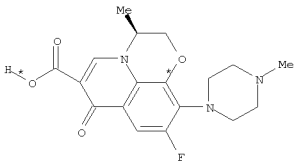
RX(3) OF 10 ...F ===> G

L3 ANSWER 27 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



F

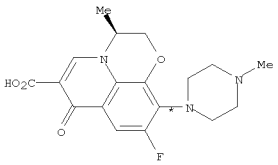
(3)



G
YIELD 57%

RX(3) RCT F 289688-79-5
RGT H 1310-58-3 KOH
PRO G 100986-85-4
SOL 64-17-5 EtOH
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

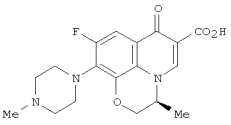
L3 ANSWER 28 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



AD
YIELD 75%

RX(10) RCT AB 100986-89-8, AC 109-01-3
PRO AD 100986-85-4
SOL 110-86-1 Pyridine
NTE stereoselective synthesis
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

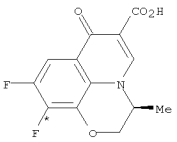
L3 ANSWER 28 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 132:22935 CASREACT
TITLE: A practical stereoselective synthesis of (S)-(-)-ofloxacin
AUTHOR(S): Yang, Yu-She; Ji, Ru-Yun; Chen, Kai-Xian
CORPORATE SOURCE: Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China
SOURCE: Chinese Journal of Chemistry (1999), 17(5), 539-544
CODEN: CJOCEV; ISSN: 1001-604X
PUBLISHER: Science Press
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



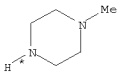
I

AB A very efficient and practical procedure for preparation of (S)-(-)-ofloxacin (I) has been developed (10 steps, overall yield ≥45%). The key step of this approach is the regioselective nucleophilic substitution of 2-position fluorine atom of 2,3,4-trifluoronitrobenzene by (S)-glycerol acetonide.

RX(10) OF 55 ...AB + AC ===> AD



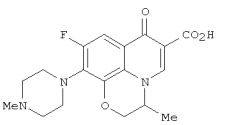
AB



AC

(10)

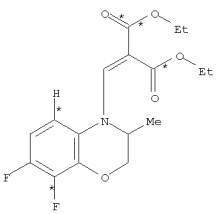
L3 ANSWER 29 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 131:214260 CASREACT
TITLE: An efficient synthesis of ofloxacin and levofloxacin from 3,4-difluoroaniline
AUTHOR(S): Adrio, Javier; Carretero, Juan C.; Ruano, Jose L. Garcia; Pallares, Antonio; Vicioso, Mercedes
CORPORATE SOURCE: Departamento de Quimica Organica, Facultad de Ciencias, Universidad Autonoma de Madrid, Madrid, 28049, Spain
SOURCE: Heterocycles (1999), 51(7), 1563-1572
CODEN: HTCYAM; ISSN: 0385-5414
PUBLISHER: Japan Institute of Heterocyclic Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



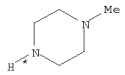
I

AB The functionalization at either C-2 or C-3 of N-(tert-butoxycarbonyl)-3,4-difluoroaniline, based on its ortho-deprotonation under different exptl. conditions, is described. This process can be readily applied to the synthesis of ofloxacin [(±)-I], levofloxacin [(S)-I], and related compds.

RX(13) OF 34 ...AN + AF ===> AO



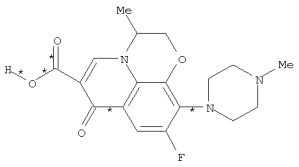
AN



AF

(13)

L3 ANSWER 29 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



AO
YIELD 67%

RX(13) RCT AN 86760-99-8, AF 109-01-3

STAGE(1)
SOL 75-05-8 MeCN

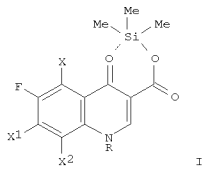
STAGE(2)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water

PRO AO 82419-36-1
NTE S-analog similarly prepd.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

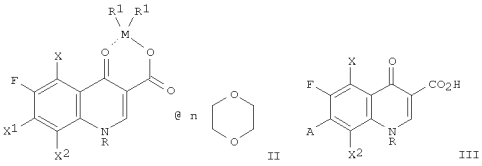
L3 ANSWER 30 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 125:247630 CASREACT
TITLE: Trimethylsilyl esters and solvates of chelates of quinoline-3-carboxylic acids, and their preparation and use in a process for quinolone antibacterials.
INVENTOR(S): Palomo Nicolau, Francisco Eugenio; Solis Oller, Jose Maria; Palomo Coll, Antonio Luis
PATENT ASSIGNEE(S): Centro Marga Para La Investigacion S.A., Spain
SOURCE: Span., 14 pp.
CODEN: SPXXAD
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
ES 2077490	A1	19951116	ES 1992-2560	19921118
ES 2077490	B1	19961016		

PRIORITY APPLN. INFO.: ES 1992-2560 19921118
OTHER SOURCE(S): MARPAT 125:247630
GI



I

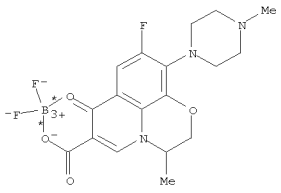


II III

AB Trimethylsilyl esters I and chelates II [X = H, NH2, NHAc, Me; X1 = halo, alkylsulfonyl, arylsulfonyloxy; X2 = H, halo, Me, OMe, OCHF2, OH, SO3H, NO2; when X = H, then X1 and X2 do not both = F; R = alkyl, cycloalkyl, alkylamino, aryl, alkylarom. group; X2R may form 5- or 6-membered heterocycle; M = B, Al; R1 = halo, acyloxy; n = 0.5-2.0] are claimed. The compds. are intermediates for quinolone antibacterials III [A = substituted amino]. For instance, 1-cyclopropyl-7-chloro-1,4-dihydro-6-fluoro-4-oxo-3-quinolinecarboxylic acid reacted with HN(SiMe3)2 in refluxing CHCl3 to give 99% I [X = X2 = H; X1 = Cl; R = cyclopropyl]. This reacted with BF3 in MeCN/1,4-dioxane mixt. at 12-15° and then 20-25° to give II [M = B; R1 = F; n unspecified; others as above] in virtually quant. yield. Reaction of this with anhyd. piperazine in DMSO at 50-65°, followed by hydrolysis with 10% NaOH at 60°, gave the corresponding III [A = piperazino], i.e. ciprofloxacin.

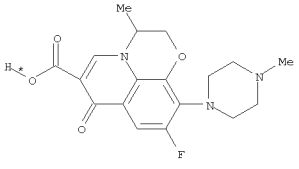
L3 ANSWER 30 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)

RX(7) OF 14 ...T ===> U



T

(7)



U

RX(7) RCT T 87531-64-4

STAGE(1)
SOL 67-68-5 DMSO

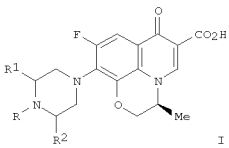
STAGE(2)
RGT M 1310-73-2 NaOH
SOL 67-68-5 DMSO, 7732-18-5 Water

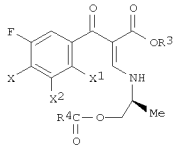
PRO U 82419-36-1
NTE 50°; 60-80°

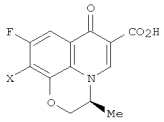
L3 ANSWER 31 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 125:195666 CASREACT
TITLE: Method for the preparation of bactericidal (-) piperazinylpyridobenzoxazine derivatives via cyclization of a 2-aminomethylene-3-oxo-3-phenylpropionate intermediate
INVENTOR(S): Kim, Youseung; Kang, Soon Bang; Park, Seonhee
PATENT ASSIGNEE(S): Korea Institute of Science and Technology, S. Korea
SOURCE: U.S., 8 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5539110	A	19960723	US 1994-321360	19941011
KR 125115	B1	19971205	KR 1994-5762	19940322

PRIORITY APPLN. INFO.: KR 1994-5762 19940322
OTHER SOURCE(S): MARPAT 125:195666
GI


I


II

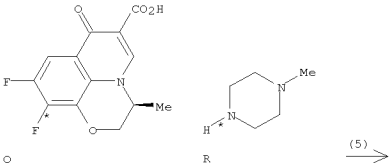

III


IV

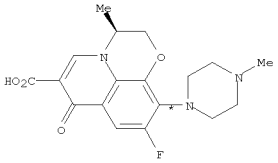
AB A method is claimed for the preparation of (-) piperazine benzoxazine derivative I
wherein R, R1 and R2 each is a hydrogen or a C1-C4 alkyl group, comprising
the steps of: reacting (+)-2-aminomethylene-3-oxo-3-phenylpropionate deriv. II wherein R3 and R4 each is a C1-C4 alkyl group, and X and X1 each
is a halogen or nitro group, and X2 is a halogen, with a base in an org. polar solvent, to give a (-) benzoxazine deriv. III wherein X is defined as above; and reacting III with a piperazine deriv. IV wherein R, R1 and R2 are defined as above, and Z is a hydrogen or trialkylsilyl group which alkyl is a C1-C4 alkyl group, in an org. polar solvent. Thus, addn. reaction of (+)-2-amino-1-propanol with Et propiolate afforded Z/E Et 3-[(1-hydroxyprop-2(S) -yl)amino]acrylate (99%) which was acetylated to Z/E Et 3-[(1-acetoxyprop-2(S)-yl)amino]acrylate (98%); acylation of the latter with 2,3,4,5-tetrafluorobenzoyl chloride afforded Z/E Et 2-(2,3,4,5-tetrafluorobenzoyl)-3-[[1-acetoxyprop-2(S)-yl]amino]acrylate (II; R4 = Me, R3 = Et; X, X1, X2 = F; 97%); treatment of the latter with KOH/THF afforded (-)-9,10-difluoro-2,3-dihydro-3(S)-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (III; X = F, 81%); substitution of the latter with N-methylpiperazine afforded 91%

(-)-9-fluoro-3(S)-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (I; R = Me, R1 = R2 = H).

RX(5) OF 15 ...O + R ===> S



L3 ANSWER 31 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



S
YIELD 91%

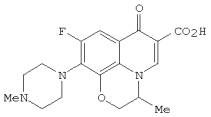
RX(5) RCT O 100986-89-8, R 109-01-3
PRO S 100986-85-4
SOL 110-86-1 Pyridine
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L3 ANSWER 32 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 121:9414 CASREACT
TITLE: Process for obtaining benzoxazines useful for the synthesis of ofloxacin, levofloxacin and derivatives
INVENTOR(S): Carretero Gonzalvez, Juan Carlo; Vicioso Sanchez, Mercedes; Garcia Ruano, Jose Luis
PATENT ASSIGNEE(S): Derivados del Etilo, S.A., Spain
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

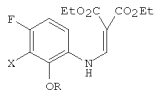
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9407873	A1	19940414	WO 1993-ES80	19931006
W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ES 2055656	A1	19940816	ES 1992-1983	19921007
ES 2055656	B1	19951116		
ES 2069500	A1	19950501	ES 1993-2080	19931004
ES 2069500	B1	19960301		
AU 9351118	A	19940426	AU 1993-51118	19931006
AU 674542	B2	19970102		
EP 619311	A1	19941012	EP 1993-921930	19931006
R: AT, BE, CH, DE, DK, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07501835	T	19950223	JP 1993-508738	19931006
KR 131914	B1	19980417	KR 1994-701925	19940607
ZA 9405098	A	19950222	ZA 1994-5098	19940713
US 5521310	A	19960528	US 1994-244455	19940831
AU 9665878	A	19961212	AU 1996-65878	19960927
AU 686955	B2	19980212		

PRIORITY APPLN. INFO.: ES 1992-1983 19921007
ES 1993-2080 19931004
WO 1993-ES80 19931006
OTHER SOURCE(S): MARPAT 121:9414
GI

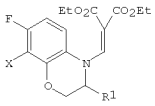
L3 ANSWER 32 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



I



II

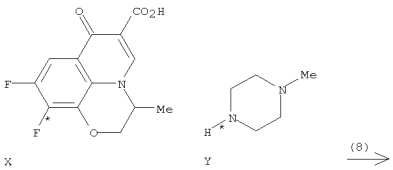


III

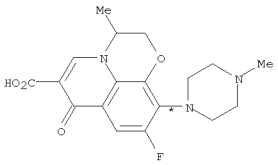
AB The antimicrobial agents ofloxacin [(±)-I], levofloxacin [(S)-I], and their derivs. and analogs are prepared in several steps. via (anilinomethylene)malonates II [R = H, CH2CH(OH)R1; R1 = H, C1-6 alkyl (especially Me), C2-6 alkenyl, aryl; X = halo (especially F)] and benzoxazines III.
For example, 3,4-difluoroaniline underwent N-tert-butoxycarbonylation (98-99%), lithiation and hydroxylation in the 2-position (89%), N-deprotection (86%), and condensation with di-Et (ethoxymethylene)malonate (80-81%) to give II [R = H, X = F]. Treatment of this with NaH, LiClO4, and propylene oxide in THF gave 65% II [R = CH2CH(OH)Me, X = F], which was cyclized by PPh3 and di-Et azodicarboxylate
(79%) to give III [R1 = Me, X = F]. Cyclization of the latter by AcOH-H2SO4 (73%), saponification by HCl-AcOH (68%), and condensation with N-methylpiperazine (79%) gave (±)-I. By using the appropriate chiral epoxide, and proceeding via enantiomeric intermediates, enantiomeric products such as (S)-I may be obtained without resolution (claimed, no examples).

RX(8) OF 48 ...X + Y ===> Z

L3 ANSWER 32 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



X Y (8)



Z

RX(8) RCT X 82419-35-0

STAGE(1)
RGT AA 109-63-7 BF3-Et2O
SOL 60-29-7 Et2O

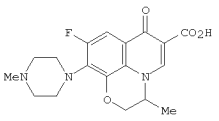
STAGE(2)
RCT Y 109-01-3
RGT AB 121-44-8 Et3N
SOL 67-68-5 DMSO

STAGE(3)
RGT AB 121-44-8 Et3N, AC 67-56-1 MeOH
SOL 67-56-1 MeOH, 7732-18-5 Water

PRO Z 82419-36-1
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 32 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)

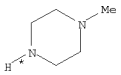
L3 ANSWER 33 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 116:255579 CASREACT
TITLE: Synthesis of fluoroquinolone antimicrobial agent ofloxacin
AUTHOR(S): Wang, Erhua; Zhou, Sangqi; Peng, Sixun
CORPORATE SOURCE: China Pharm. Univ., Nanjing, 210009, Peop. Rep. China
SOURCE: Zhongguo Yiyao Gongye Zazhi (1991), 22(9), 385-7
CODEN: ZYGZEA; ISSN: 1001-8255
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
GI



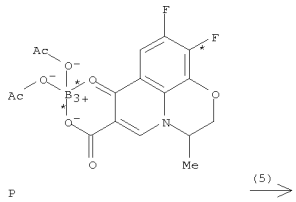
I

AB The title compound (I) was prepared in 5 steps in >30% overall yield starting
from 2,3,4-trifluoronitrobenzene.

RX(5) OF 20 ...S + P ===> T

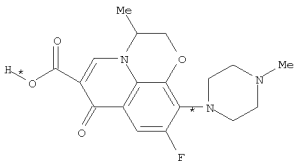


S



P (5)

L3 ANSWER 33 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



T
YIELD 71%

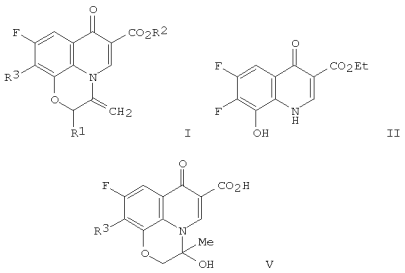
RX(5) RCT S 109-01-3, P 97746-91-3

STAGE(1)
RGT U 121-44-8 Et3N
SOL 67-68-5 DMSO

STAGE(2)
SOL 7732-18-5 Water, 67-56-1 MeOH

PRO T 82419-36-1
NTE RING-OPENED REACTANT ISOMER ALSO PRESENT

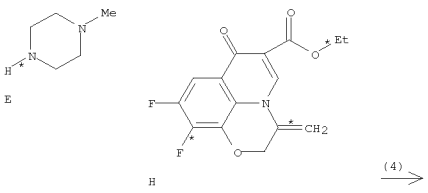
L3 ANSWER 34 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 116:214460 CASREACT
TITLE: Preparation of some 2,3-dihydro-7-oxo-7H-pyrido[1,2,3-de][1,4]benzoxazine derivatives
AUTHOR(S): Radl, Stanislav; Moural, Jaroslav; Bendova, Radoslava
CORPORATE SOURCE: Res. Inst. Pharm. Biochem., Prague, 130 60, Czech.
SOURCE: Collection of Czechoslovak Chemical Communications (1992), 57(1), 216-18
CODEN: CCCCAK; ISSN: 0010-0765
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



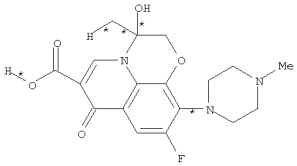
AB Ofloxacin analog I (R1 = Me, R2 = H, R3 = 4-methylpiperazino) were prepared by cyclocondensation of 3-bromo-1-butyne with 8-hydroxquinolone II to give difluoro adduct I (R1 = Me, R2 = Et, R3 = F) (III). Treatment of III with 1-methylpiperazine, followed by basic hydrolysis gave I (R1 = Me, R2 = H, R3 = 4-methylpiperazino). Acidic hydrolysis of I (R1 = H, R2 = Et, R3 = F) (IV) gave alc. V (R3 = F). Similarly, treatment of IV with 1-methylpiperazine followed by acidic hydrolysis gave V (R = 4-methylpiperazino).

RX(4) OF 5 E + H ===> L

L3 ANSWER 34 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



E H (4)



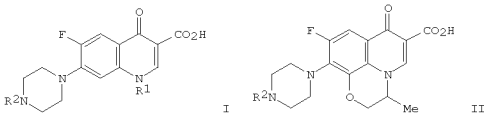
L
YIELD 28%

RX(4) RCT E 109-01-3, H 90180-70-4
RGT J 64-19-7 AcOH, K 7647-01-0 HCl
PRO L 140701-05-9

L3 ANSWER 35 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 116:194351 CASREACT
TITLE: Preparation of piperazinylquinolone derivatives
PATENT ASSIGNEE(S): Korea Institute of Science and Technology, S. Korea
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

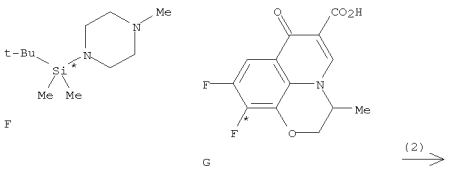
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 03279361	A	19911210	JP 1990-252044	19900925
JP 07005562	B	19950125		
DE 4100855	A1	19911002	DE 1991-4100855	19910114
PRIORITY APPLN. INFO.:			KR 1990-4115	19900327

OTHER SOURCE(S): MARPAT 116:194351
GI



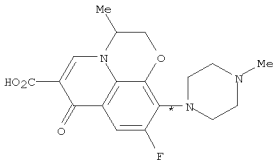
AB Title compound I and II (R1 = alkyl, cycloalkyl; R2 = H, alkyl), useful as bactericides, were prepared Thus, stirring 1-ethyl-6-fluoro-7-chloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid with 1-(tert-butyldimethylsilyl)piperazine and tetrabutylammonium fluoride trihydrate in pyridine at 80° for 2 h gave 90% I (R1 = Et, R2 = H).

RX(2) OF 2 F + G ===> H



F G (2)

L3 ANSWER 35 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



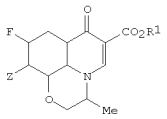
H
YIELD 94%

RX(2) RCT F 138938-63-3, G 82419-35-0
RGT D 87749-50-6 Bu4N.F.3H2O
PRO H 82419-36-1
SOL 110-86-1 Pyridine

L3 ANSWER 36 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 110:75530 CASREACT
TITLE: Process for preparation of racemic and optically active ofloxacin and related derivatives
INVENTOR(S): Mitscher, Lester A.; Chu, Daniel T.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4777253	A	19881011	US 1986-858532	19860425
US 4826985	A	19890502	US 1988-216063	19880707

PRIORITY APPLN. INFO.: US 1986-858532 19860425
OTHER SOURCE(S): MARPAT 110:75530
GI

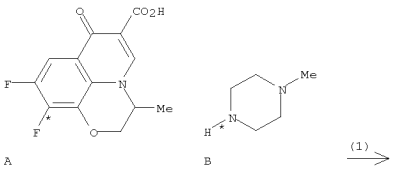


I

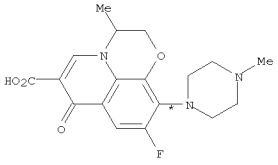
AB The title compds. I (R1 = H, C1-4 alkyl, PhCH2; Z = R4R5N; R4, R5 = H, alkanoyl, alkanoylamido, substituted amino; R4R5N = (un)substituted aliphatic heterocyclyl) (wherein the the racemate of ofloxacin exhibits antibacterial properties) were prepared (-)-I (R1 = Et; Z = F) (preparation given) in pyridine was added to 1-methylpiperazine, the mixture heated to 55°, and after workup, the solid obtained was dissolved in THF and NaOH solution to give (-)-I (R1 = H; Z = 4-methylpiperazinyl).

RX(1) OF 102 ...A + B ===> C

L3 ANSWER 36 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



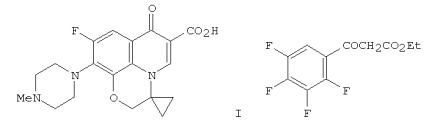
A B (1)



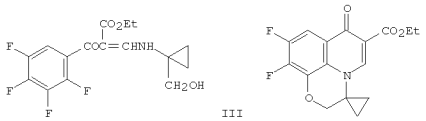
C

RX(1) RCT A 82419-35-0, B 109-01-3
PRO C 82419-36-1
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 37 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 109:92905 CASREACT
TITLE: Synthesis and bacterial DNA gyrase inhibitory properties of a spirocyclopropylquinolone derivative
AUTHOR(S): Wentland, Mark P.; Perni, Robert B.; Dorff, Peter H.; Rake, James B.
CORPORATE SOURCE: Dep. Med. Chem. Microbiol., Sterling-Winthrop Res. Inst., Rensselaer, NY, 12144, USA
SOURCE: Journal of Medicinal Chemistry (1988), 31(9), 1694-7
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I II

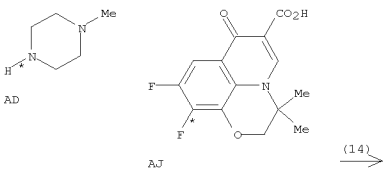


III IV

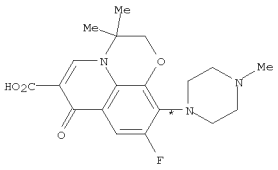
AB A novel conformationally restricted 1-cyclopropylquinlone, I, that incorporates structural features of both ofloxacin and ciprofloxacin was prepared from ester II via cyclopropyl derivative III. Cyclization of III with K2CO3-DMF gave 66% pyridobenzoxazine derivative IV. Ester hydrolysis of IV followed by substitution with N-methylpiperazine gave I. I was a DNA gyrase inhibitor having potency similar to ofloxacin but less than ciprofloxacin. The cellular inhibitory and in vivo antibacterial potencies of I were less than those of the two reference agents.

RX(14) OF 113 ...AD + AJ ===> AL

L3 ANSWER 37 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



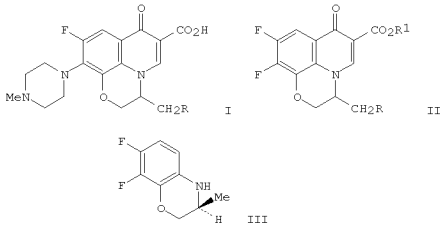
AD AJ (14)



AL
YIELD 70%

RX(14) RCT AD 109-01-3, AJ 107358-79-2
PRO AL 107359-24-0
SOL 110-86-1 Pyridine

L3 ANSWER 38 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 108:131711 CASREACT
TITLE: Synthesis and antibacterial activities of optically active ofloxacin and its fluoromethyl derivative
AUTHOR(S): Atarashi, Shohgo; Yokohama, Shuichi; Yamazaki, Kenichi; Sakano, Katsuichi; Imamura, Masazumi; Hayakawa, Isao
CORPORATE SOURCE: Res. Inst., Daiichi Seiyaku Co., Ltd., Tokyo, 134, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1987), 35(5), 1896-902
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



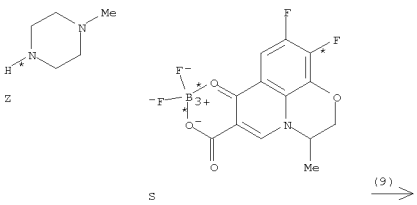
I II

III

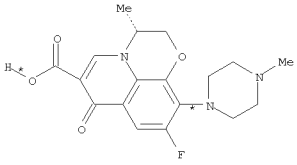
AB The enantiomers of (±)-ofloxacin [(±)-I; R = H] were prepared in 7 steps from (±)-(hydroxymethyl)oxopyridobenzoxazinecarboxylate [(±)-II; R = OH, R1 = Et]. HPLC resolution of (±)-II [R = O2CC6H3(NO2)2-3,5, R1 = Et], followed by monosapon., iodination, and radical deiodination of each enantiomer gave (+)- and (-)-II (R = H; R1 = Et). Ester hydrolysis, complexation with BF3.OEt2, and monosubstitution with 1-methylpiperazine gave (+)- and (-)-I (R = H). A similar sequence with fluorination rather than iodination-deiodination gave (+)- and (-)-I (R = F). (±)-I (R = H, F) and (+)- and (-)-I (R = H, F) were tested for bactericidal activity. (-)-I (R = H, F) were ca. twice as active as (±)-I (R = H, F) resp., and (±)-I (R = H, F) were considerably more active than (+)-I (R = H, F), resp. The structure of (S)-methylbenzoxazine III, prepared by resolution of its racemate, was determined by x-ray crystallog. and was related by synthesis to that of (-)-I (R = H, F).

RX(9) OF 67 ...Z + S ===> AA

L3 ANSWER 38 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



Z S (9)



AA

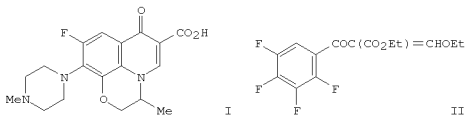
RX(9) RCT Z 109-01-3, S 113348-93-9

STAGE(1)
SOL 67-68-5 DMSO

STAGE(2)
CAT 121-44-8 Et3N
SOL 67-56-1 MeOH

PRO AA 100986-86-5

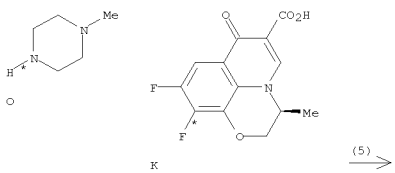
L3 ANSWER 39 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 107:198206 CASREACT
TITLE: Chiral DNA gyrase inhibitors. 2. Asymmetric synthesis and biological activity of the enantiomers of 9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (ofloxacin)
AUTHOR(S): Mitscher, Lester A.; Sharma, Padam N.; Chu, Daniel T. W.; Shen, Linus L.; Pernet, Andre G.
CORPORATE SOURCE: Dep. Med. Chem., Kansas Univ., Lawrence, KS, 66045, USA
SOURCE: Journal of Medicinal Chemistry (1987), 30(12), 2283-6
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I II

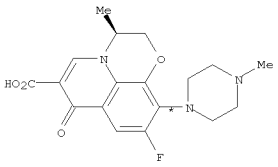
AB A short and efficient synthesis of the two optical antipodes of ofloxacin (I) from (R)- and (S)-alaninol and (tetrafluorobenzoyl)alkene II is reported. In vitro testing of the products against a range of bacteria and in an assay system incorporating purified DNA gyrase from different bacterial species demonstrates that the S-(-) enantiomer is substantially the more active.

RX(5) OF 37 ...O + K ===> P



O K (5)

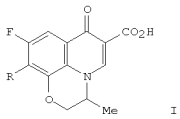
L3 ANSWER 39 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



P
YIELD 83%

RX(5) RCT O 109-01-3, K 100986-89-8
RGT Q 110-86-1 Pyridine
PRO P 100986-85-4

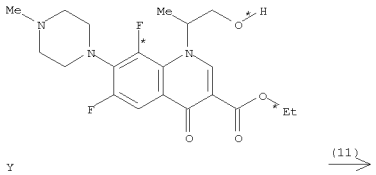
L3 ANSWER 40 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 107:39724 CASREACT
TITLE: Pyridonecarboxylic acids as antibacterial agents. Part 6. A new synthesis of 7H-pyrido[1,2,3-de][1,4]benzoxazine derivatives including an antibacterial agent, ofloxacin
AUTHOR(S): Egawa, Hiroshi; Miyamoto, Teruyuki; Matsumoto, Junichi
CORPORATE SOURCE: Res. Lab, Dainippon Pharm. Co., Ltd., Suita, 564, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1986), 34(10), 4098-102
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

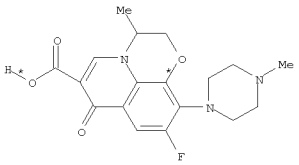
AB A new method for the synthesis of 7H-pyrido[1,2,3-de][1,4]benzoxazine derivs. I (R = F, 4-methyl-1-piperazinyl) was developed. The method is characterized by the intramol. cyclization of 1-(1-hydroxyprop-2-yl)-8-fluoro-4-quinolones which are prepared in three or four steps from Et 2,3,4,5-tetrafluorobenzoylacetate.

RX(11) OF 31 ...Y ===> AA



Y

L3 ANSWER 40 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



AA
YIELD 47%

RX(11) RCT Y 113933-54-3

STAGE(1)
RGT N 7646-69-7 NaH
SOL 123-91-1 Dioxane

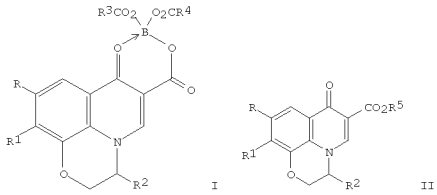
STAGE(2)
RGT AB 1310-73-2 NaOH
SOL 7732-18-5 Water

PRO AA 82419-36-1

L3 ANSWER 41 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 103:123491 CASREACT
TITLE: Oxazines
PATENT ASSIGNEE(S): Daiichi Seiyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 60078986	A	19850504	JP 1983-188138	19831007
JP 03072073	B	19911115		
PRIORITY APPLN. INFO.:			JP 1983-188138	19831007

GI

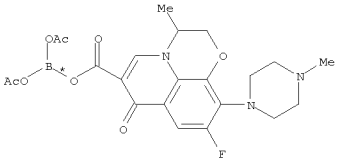


I II

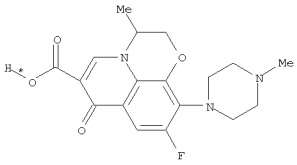
AB Chelate dissociation of I [R = halo; R1 = (4-alkyl)-1-piperazinyl; R2 = H, alkyl; R3, R4 = aryl, alkyl, haloalkyl], prepared from I (R1 = halo) and (alkyl)piperazine, gave II having antibacterial activities. Thus, refluxing H3BO3, (EtCO)2O, and II (R = R1 = F; R2 = Me; R5 = Et) gave 95.2% I (R3 = R4 = Et), which was stirred with 4-methylpiperazine and neutralized to give 83.9% II (R1 = 4-methyl-1-piperazinyl; R5 = H).

RX(1) OF 2 A ===> B

L3 ANSWER 41 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



A



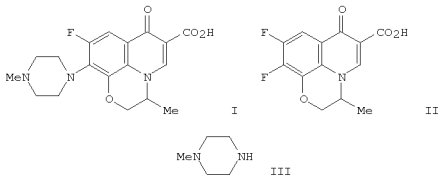
B

RX(1) RCT A 97847-98-8
PRO B 82419-36-1

L3 ANSWER 42 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 103:6370 CASREACT
TITLE: Pyrido[1,2,3-de][1,4]benoxazine derivatives as bactericides
PATENT ASSIGNEE(S): Daiichi Seiyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 60034968	A	19850222	JP 1984-134470	19840629
JP 61039312	B	19860903		
JP 62187473	A	19870815	JP 1987-12254	19870123
JP 62056154	B	19871124		

PRIORITY APPLN. INFO.: JP 1984-134470 19840629
GI



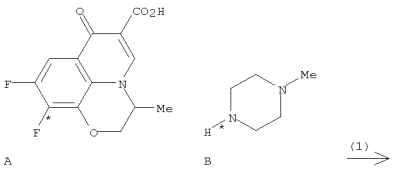
I II

III

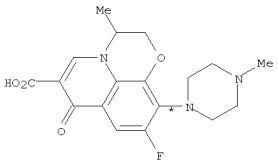
AB Pyridobenzoxazine derivative (I) and its salts were prepared I and its salts showed bactericidal activities against gram-pos. and gram-neg. bacteria at 0.05-1.56 μg/mL, vs. 1.56-100 μg/mL for pipemidic acid. Thus, heating a mixture of 1.0 g difluoro compound II with 2.85 g III in Me2SO at 100-110° with stirring gave 550 mg I.

RX(1) OF 1 A + B ===> C

L3 ANSWER 42 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



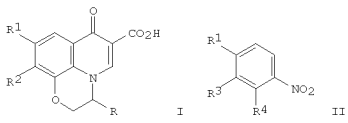
A B



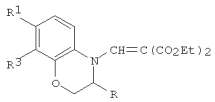
C

RX(1) RCT A 82419-35-0, B 109-01-3
PRO C 82419-36-1

L3 ANSWER 43 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 102:166678 CASREACT
TITLE: Synthesis and antibacterial activities of substituted 7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acids
AUTHOR(S): Hayakawa, Isao; Hiramitsu, Tokiyuki; Tanaka, Yoshiaki
CORPORATE SOURCE: Res. Inst., Daiichi Seiyaku Co., Ltd., Tokyo, 134, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1984), 32(12), 4907-13
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I II

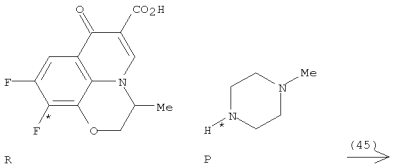


III

AB Title compds. I [R = H, Me; R1 = F, Cl; R2 = (substituted) piperazino, piperidino, diazepino, pyrrolidino, etc.] (44 compds.) were prepared from nitrobenzenes II (R1, R3, R4 = F, F, F; Cl, F, Cl; F, Cl, F) via benzoxazines III. I (R = Me, R1 = F, R2 = 4-methyl-1-piperazinyl) (DL-8280) showed potent antibacterial activity against Gram-pos. and -neg. pathogens, including Pseudomonas aeruginosa, and its metabolic disposition was shown in sep. expts. to be favorable.

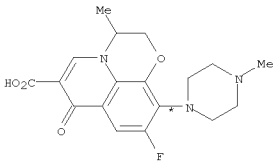
RX(45) OF 183 ...R + P ===> CK

L3 ANSWER 43 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



R P

(45)



CK

RX(45) RCT R 82419-35-0, P 109-01-3
PRO CK 82419-36-1
SOL 67-68-5 DMSO

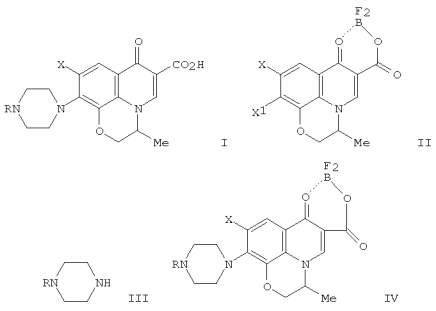
L3 ANSWER 44 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 99:175804 CASREACT
TITLE: Pyridobenzoxazine derivatives
PATENT ASSIGNEE(S): Daiichi Seiyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 58043977	A	19830314	JP 1981-141919	19810909
JP 01048910	B	19891020		
FI 8203024	A	19830310	FI 1982-3024	19820901
FI 76345	B	19880630		
FI 76345	C	19881010		
DK 8203997	A	19830310	DK 1982-3997	19820907
DK 158268	B	19900423		
DK 158268	C	19901015		
DD 203719	A5	19831102	DD 1982-243116	19820908
PL 130881	B1	19840929	PL 1982-238177	19820908
JP 63119487	A	19880524	JP 1987-234466	19870918
JP 02014356	B	19900406		
FI 8801403	A	19880324	FI 1988-1403	19880324
FI 80463	B	19900228		
FI 80463	C	19900611		
DK 8801735	A	19880329	DK 1988-1735	19880329
JP 01038092	A	19890208	JP 1988-175747	19880714
JP 02015554	B	19900412		
HR 9300085	B1	20021031	HR 1993-85	19930201

PRIORITY APPLN. INFO.: JP 1981-141919 19810909
FI 1982-3024 19820901
JP 1987-234466 19870918
YU 1988-746 19880414

GI

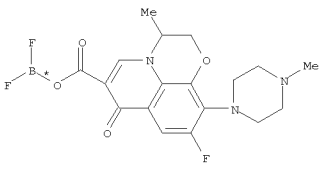
L3 ANSWER 44 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



I II III IV

AB Pyridobenzoxaxine derivs. I (R, X = Me, Cl; Me, F; H, F) were prepared by amination of II (X1 = halo) with III followed by decomposition of the resulting IV. Min. inhibition concns. of I were shown against E. coli, Sh. Flexneri, Pr. Vulgaris, and 9 other bacteria strains. Thus, reaction of a mixture of II (X = X1 = F) 1, III (R = Me) 0.46, and Et3N 0.62 g in Me2SO 3 h at room temperature gave 98.9 % IV (R = Me, X = F), which (1 g) was refluxed with 0.5 g Et3N in 95 % EtOH 6 h to give 86 % I (R = Me, X = F).

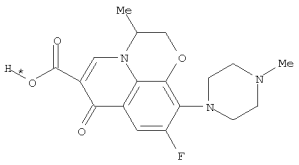
RX(1) OF 6 ...A ===> B



A

(1)

L3 ANSWER 44 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



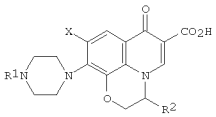
B

RX(1) RCT A 87558-89-2
PRO B 82419-36-1

L3 ANSWER 45 OF 45 CASREACT COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 99:85015 CASREACT
TITLE: Anti-acid-fast bacteria agents
PATENT ASSIGNEE(S): Daiichi Seiyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 58062113	A	19830413	JP 1981-160717	19811008
JP 01022246	B	19890425		

PRIORITY APPLN. INFO.: JP 1981-160717 19811008
GI

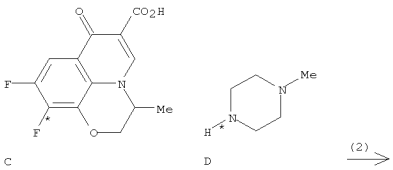


I

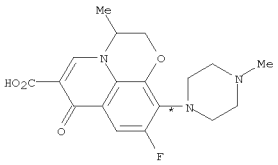
AB I (R1 and R2 = H or alkyl; X = halo), especially 9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3,de][1,4]benzoxazine-6-carboxylic acid (DL-8280) or its salts, are effective against acid-fast bacteria, especially Mycobacterium. The growth of various Mycobacterium species tested in conventional culture media was effectively inhibited in the presence of DL-8280. With the exception M. avium, the min. inhibitory concns. of DL-8280 for other mycobacteria, including M. bovis, M. kansasii, M. intracellulare, M. fortuitum, and M. marinum, were ≤1.56 μg/mL.

RX(2) OF 22 ...C + D ===> E

L3 ANSWER 45 OF 45 CASREACT COPYRIGHT 2009 ACS on STN (Continued)



C D (2)



E

RX(2) RCT C 82419-35-0, D 109-01-3
PRO E 82419-36-1